

### **Remarks**

Claim 30 has been amended to specify that "each strand comprises 17-25 nucleotide monomers". Support for the amendment is found, for example, in paragraph [120] of the application as published. Claims 58 and 59 have been added. Support for these claims is found in paragraphs [114] and [120] respectively. No new matter has been added

### **Rejections Under 35 U.S.C. §102(b)**

Claims 30-32, 40, 44-48, 54, 56 and 57 were rejected as anticipated by Braasch et al. (*Biochemistry* 42:7967, 2003).

Braasch discloses four siRNA molecules that have been modified to include an LNA. These four are referred to as L3, L5, L6 and L7. As the Examiner correctly points out, none of these molecules have a modified RNA nucleotide, for example, LNA located at position 14 counting from the 5' end of the sense strand. Claim 30 has been amended to require a modified RNA nucleotide at this position. Of course, modified RNA nucleotides can be present at other positions, as indicated by the specification and by dependent claim 30. Because Braasch does not disclose a modified RNA nucleotide at position 14 of the sense strand counting from the 5' end, it cannot anticipate the present claims

Claims 30-32, 40, 44-48, 54, 56 and 57 were rejected as anticipated by McSwiggen et al. (US 2005/0261212). As the Examiner correctly points out, McSwiggen does not disclose a siRNA molecule having a modified RNA nucleotide, for example, LNA located at position 14 counting from the 5' end of the sense strand. Claim 30 has been amended to require a modified RNA nucleotide at this position. Of course, modified RNA nucleotides can be present at other positions, as indicated by the specification and by dependent claim 30. Because McSwiggen does not disclose a modified RNA nucleotide at position 14 of the sense strand counting from the 5' end, it cannot anticipate the present claims.

In view of the forgoing, Applicant requests that the rejections under 35 U.S.C. §102(b) be withdrawn.

### **Rejections Under 35 U.S.C. §103**

Claims 30-32, 40, 44-48, 54, 56 and 57 were rejected as obvious in view of Braasch et al. The Examiner argued that even though Braasch does not disclose a siRNA molecule having a modified RNA such as LNA located at position 14 of the sense strand counting from the 5' end, it would have been obvious to make and use such a siRNA because "Braasch et al. demonstrate that LNA modifications can be placed throughout the sense and antisense strand without diminishing efficacy."

Applicant disagrees that Braasch teaches that LNA can be placed throughout the sense and antisense strands without decreasing efficiency. Instead, Braasch found that three of the four siRNA having internal (as opposed to 3' or 5') LNA (L3, L5 and L7) were essentially inactive, while one (L6) was active. Braasch states that the reasons for the different efficiencies "of L6 relative to L3, L5 and L7 is not obvious because they possess similar T<sub>m</sub> values and have LNA substitutions at similar positions". After analyzing additional data, Braasch concludes that "to maximize the likelihood that potent inhibition of gene expression will be maintained, LNA substitutions should be kept to a minimum and should not infringe on the central region of the RNA." Thus, Braasch would discourage one from placing a modified RNA nucleotide such as an LNA at position 14 of the sense strand, which for a siRNA having 17-25 nucleotide monomers in each strand, as required by the present claims, would most often place the LNA in the central region of the siRNA. This is particularly true in the case of claim 58 which requires that each strand of the siRNA have 20-22 nucleotide monomers. In this situation, an LNA located at position 14 would be located in about the central 1/3 of the molecule. However, as can be seen from Figure 2 of the present application, placing the LNA at position 14 of the sense strand (counting from the 5' end) of a 21-mer siRNA resulted in a molecule having good activity. Thus, the presently claimed molecules are contrary to the teachings of Braasch.

Claims 30-32, 40, 44-48, 54, 56 and 57 were rejected obvious in view of McSwiggen. The Examiner argued that even though McSwiggen does not disclose a siRNA molecule having a modified RNA such as LNA located at position 14 of the sense strand counting from the 5' end, it would have been a matter of routine optimization and thus obvious to make and use such a siRNA because "McSwiggen teach that functional siRNA can comprise LNA modifications throughout the siRNA."

However, while McSwiggen suggests that LNA can be used at up to 10 positions from either the 5' or the 3' end of an siRNA molecule, McSwiggen does not disclose any examples of siRNA with LNA. Moreover, despite McSwiggen comments, Braasch et al. teaches that LNA should be preferably excluded from the central region of siRNA. Thus, one skilled in the art would rely on the actual experimental data of Braasch -- which suggests excluding LNA from the central region of siRNA -- rather than the speculation of McSwiggen. As explained above, the presently claimed molecules are contrary to the teachings of Braasch and are not obvious in view of the cited references.

Applicant wishes to draw the Examiner's attention to claim 58 which specifies that the siRNA not have a modified RNA at the 5' end of the antisense strand. This is contrary to Braasch and to McSwiggen, which suggests that LNA are preferably at the ends of the siRNA.

Applicant also wishes to draw the Examiner's attention to claim 59 which specifies that "the antisense strand optionally comprises an LNA at one or more of positions 2, 3, and 4 counting from the 3' end and does not comprise an LNA at any other position." Neither reference cited by the Examiner suggests the desirability of having an LNA in a central region of the sense strand while excluding them from the central region of the antisense strand.

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In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

### **Conclusion**

The fee in the amount of \$1110 for the Petition for Extension of Time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

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